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Deferoxamine Intradermal Delivery Patch for Treatment of a Radiation Therapy Associated Breast Wound

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Abstract

Purpose: Radiation therapy is used in over 60% of cancer patients and can lead to radiation dermatitis, radiation induced fibrosis, hyperpigmentation, telangiectasias, fat necrosis, and poor wound healing. Deferoxamine (DFO) is an iron-chelating agent that has been used systemically to treat iron overload conditions and more recently been studied to treat radiation fibrosis. Through iron chelation, DFO stabilizes hypoxia inducible factor-1α, driving downstream upregulation of angiogenic factors, and reduces formation of reactive oxygen species, thereby offering a potential therapy for radiation associated chronic wounds. The purpose of this work was to describe treatment of a refractory wound following radiation treatment that had failed conventional therapy.

Methods: The patient is a 71-year-old female with inflammatory breast cancer that developed a radiation related wound after mastectomy, chemotherapy, and radiation therapy. The wound did not show any signs of improvement with five months of wound care and risk factor modification. The patient was offered treatment with a topical Deferoxamine Intradermal Delivery Patch through the FDA single patient investigative new drug pathway.

Results: After two weeks of treatment, the wound healed. Additionally, serum was collected at cessation of therapy and 5 weeks after, with both samples showing no significant systemically detectible level of the drug to be present. Subjectively the patient reported improvement in appearance and quality of the skin.

Conclusion: Topical deferoxamine is a promising therapy for radiation wounds. Although this report is limited to a single patient experience, we believe this work is important in describing the first in-human use of topical deferoxamine to heal a radiation therapy associated wound.

Keywords: Deferoxamine; Radiation; Wound Healing; Chronic Wounds; Radiation Wounds; Iron Chelation

Abbreviations: DFO: Deferoxamine; DIDP: Deferoxamine Intradermal Delivery Patch; FDA: Food and Drug Administration; HIF-1α: Hypoxia Inducible Factor-1α

Introduction

Radiation therapy is utilized as an adjuvant therapy in over 60% of cancer patients. [1] It is estimated that by 2030, there will be over 2 million radiation-treated breast cancer survivors alone. [2] For breast cancer specifically, radiation therapy effectively reduces cancer recurrence and mortality. [3] Unfortunately, radiation therapy is associated with both systemic and local side effects. The local impact of radiation includes radiation dermatitis, radiation-induced fibrosis, hyperpigmentation, telangiectasias, fat necrosis, and poor wound healing. [4,5]

Deferoxamine (DFO) is an iron-chelating agent that has been approved by the US Food and Drug Administration (FDA) for the treatment of acute iron intoxication and chronic iron overload due to transfusion-dependent anemias. [6] Notably, FDA approval was granted for intramuscular, subcutaneous, and intravenous administration. Topical DFO has since been studied for the treatment of radiation induced fibrosis [4], diabetic wounds [7], and sickle cell related wounds [8]. The mechanism of action in the treatment of iron intoxication/overload is iron chelation. Whereas, the mechanism of action in the treatment of radiation induced fibrosis and wound healing is likely a combination of hypoxia-inducible factor-1α (HIF-1α) activation and stabilization, neovascularization, and a reduction in reactive oxygen species. [4,7]

We present a patient that developed a non-healing radiation therapy associated wound with little improvement over five months, which then healed following two weeks of topical DFO treatment.

Methods

The patient is a 71-year-old female with inflammatory breast carcinoma diagnosed in 1981. Initial therapy included radiation and 6 cycles of chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil. She did well for many years until she developed new malignant disease in the right axilla and left breast in July 2020. She underwent 6 cycles of combination chemotherapy and immunotherapy from August 2020 to January 2021, including carboplatin (5 of 6 cycles), docetaxel (2 of 6 cycles), and pembrolizumab (Keytruda). The planned number of chemotherapy cycles was limited by toxicities. In January 2021 she underwent left extended mastectomy with sentinel lymph node biopsy. Pathology showed primary triple negative breast cancer, and the left and right sentinel lymph node biopsies showed metastatic disease. She underwent autologous breast reconstruction with a free flap from abdominal tissue in February 2021. After breast reconstruction she received 5000 cGy of radiation therapy over 25 fractions. After undergoing radiation therapy, in October of 2021, the patient developed a draining wound at the superior-medial aspect of the abdominal tissue flap measuring 0.5 cm^2 (Figure 1). The wound did not improve with local wound care and risk factor modification. Since there were no available alternatives, approval was obtained for treatment with a Deferoxamine Intradermal Delivery Patch (DIDP) through the FDA single patient investigative new drug pathway.

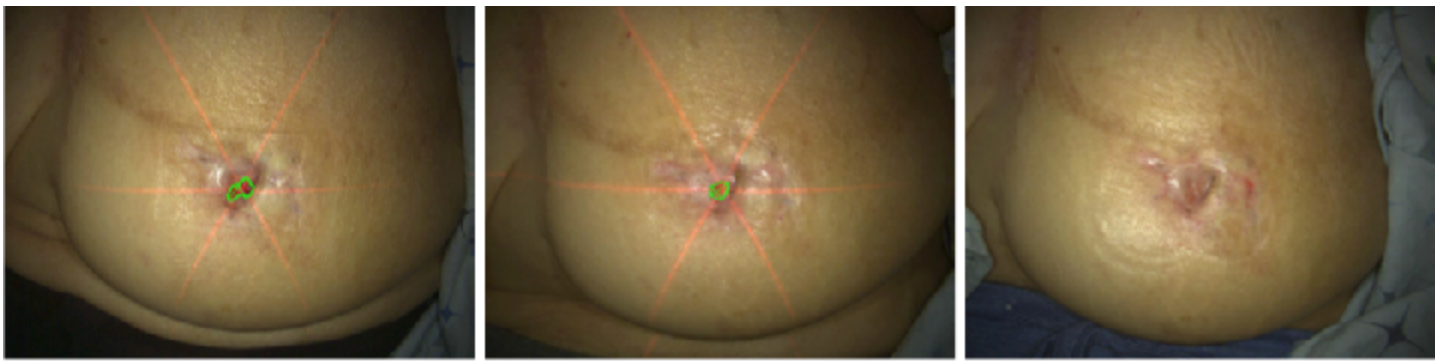

Figure 1: Radiation breast wound before and after treatment with topical deferoxamine.

Other medical history included hysterectomy (1985), mitral valve stenosis, tricuspid valve regurgitation, atrial fibrillation, and aortic stenosis treated with a total aortic valve replacement (2012).

Treatment with DIDP was started on March 10, 2022. The patch was applied to the wound and the surrounding skin (Figure 2). The DIDP measured 7.5 x 6 cm and contained 1 mg DFO per 1 cm2, formulated to release DFO over 24 hours in a controlled manner. As such, the patch was changed daily by the patient at home and secured with an adhesive dressing. Treatment continued until the wound was healed.

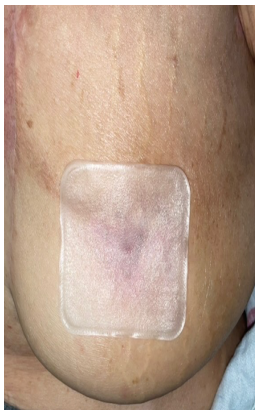

Figure 2: Deferoxamine Intradermal Delivery Patch applied to radiation breast wound.

Results

After two weeks of treatment the wound had healed (Figure 1). The patient was seen again five weeks after healing to ensure the wound had not recurred. Serum DFO levels were drawn on cessation of therapy and 5 weeks after. High powered liquid chromatography was performed by Frontage Laboratories, Inc. On cessation of therapy, serum level for DFO was < 1.00 ng/ml. Five weeks after cessation of therapy, serum DFO level was 1.39 ng/ml.

The "Radiation" and "Physical Well Being: Chest" instruments on the Breast-Q questionnaire were used before and after treatment. The patient reported improvements in both the appearance and quality of the skin (Tables 1 and 2).

Question	Before Treatment	After Treatment
a) Your radiated breast skin looking different (e.g., too dark too light)?	A little	A little
b) Marks on your breast skin caused by radiation (e.g., small visible blood vessels)?	A lot	A little
c) Your radiated breast skin feeling dry?	Not at all	Not at all
d) Your radiated breast skin feeling sore (sensitive) when touched (e.g., changes in water temperature when you bathe/shower)?	Not at all	Not at all
e) Your radiated breast skin feeling unnaturally thick (rough, tough) when you touch it?	A lot	A little
f) Your radiated breast skin feeling irritated by clothing that you wear?	Not at all	Not at all

Table 1: Adverse Effects of Radiation.

Question	Before Treatment	After Treatment
a) Pain in the muscles of your chest?	None of the time	None of the time
b) Difficulty lifting or moving your arms?	Some of the time	Some of the time
c) Difficulty sleeping because of discomfort in your breast area?	None of the time	None of the time
d) Tightness in your breast area?	None of the time	None of the time
e) Pulling in your breast area?	Some of the time	Some of the time

f)	Nagging feeling in your breast area?	Some of the time	Some of the time
g)	Tenderness in your breast area?	None of the time	None of the time
h)	Sharp pains in your breast area?	None of the time	None of the time
i)	Aching feeling in your breast area?	None of the time	None of the time
j)	Throbbing feeling in your breast area?	None of the time	None of the time
k)	Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery?	None of the time	None of the time

Table 2: Physical Well Being: Chest.

Discussion

We present the first in-human use of topical DFO in the treatment of a radiation therapy associated wound. Subjectively, this patient suffered from both a radiation ulcer as well as skin changes suggesting radiation induced fibrosis. Surprisingly, the wound healed within two weeks of treatment and the patient reported improvement in both appearance and quality of the skin. We hypothesize that the improvement in healing and skin quality observed were a result of DFO treating the wound as well as surrounding radiation induced fibrosis.

Radiation is well known to disrupt the complex milieu of cytokines crucial to the inflammatory, proliferation, and remodeling phases of wound healing leading to erythema, hyperpigmentation, hair loss, skin atrophy, telangiectasias, fibrosis, and ulcers. [9] Moreover, radiation-induced fibrosis further impairs wound healing via cellular depletion, aberrant collagen deposition, prolonged inflammation, reduced growth factor expression in keratinocytes (e.g. transforming growth factor-beta, fibroblast growth factors-1 and -2, and vascular endothelial growth factor), and microvascular damage. [4] DFO has been well studied in diabetic wounds [7] and sickle cell-related wounds [8]. However, to date, the published data suggesting improvement in radiation-related wounds/ulcers with DFO treatment is limited. Snider et al. showed that 20 days of topical treatment with DFO significantly decreased skin ulceration and fibril disorganization in radiation-induced ulcers following delivery of 28 Gy fractionated radiation over tissue expanders on the backs of Sprague-Dawley rats. [10] Lintel et al. showed that topical DFO treatment accelerated wound closure and reduced the frequency of healing failure in radiation wounds on the dorsum of wild-type mice that received 30 Gy of radiation and a stented excisional wound. [11] Additionally, DFO increased collagen density and improved collagen fiber organization more closely resemble healed wounds in non-irradiated tissue. [11] This present report, as well as the robust body of preclinical literature on DFO and radiation-induced fibrosis, establishes a precedent for using DFO for radiation therapy-associated wounds. We hope that the case presented here will lead to further research in this area.

Limitations of our report include this being a single patient experience with no comparison wound either in this study or comparable one in the literature, given the variable healing trajectory of wounds in radiated tissue. This study is observational alone, and we can only speculate as to causation or mechanism of action based on previous literature. Randomized clinical trials are required to determine if topical DFO can improve healing of radiation therapy associated wounds. There are currently on-going clinical trials using DFO to treat sickle cell wounds and a single patient trial for a patient with a beta-thalassemia wound, which can be referenced on clinicaltrials.gov.

Conclusion

In conclusion, DFO has the potential to improve radiated tissue healing by HIF-1α stabilization with downstream angiogenic growth factor upregulation and reduction in levels of reactive oxygen species. Amelioration of radiation induced fibrosis in surrounding tissue may also be of benefit. [4,7] We are pleased that despite approximately half a year of little improvement in healing, our patient's wound healed after two weeks of treatment with DFO. We eagerly await further work to elucidate the role of DFO in radiation wound healing and radiation induced fibrosis.

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Ethical Guidelines: This study was conducted under the ethical guidelines and approval of the US Food and Drug Administration and Institutional Review Board.

Conflict of Interest: The authors hold no conflict of interest.

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